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PERIOPERATIVE CLOSED-LOOP CONTROL OF ANALGESIA IN HUMANS

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Abstract

We present a new paradigm for intraoperative closed-loop control of analgesia in humans. The infusion rate of the opiate alfentanil is the manipulated variable which is administered intravenously through a Computer Controlled Infusion Pump (CCIP). The two regulated outputs are the patient's Mean Arterial Pressure (MAP) and the drug concentration in the plasma. Maintaining MAP within acceptable ranges improves the patient's reactions to surgical stimulation. Tracking plasma concentrations enables anesthesiologists to titrate analgesic administration to other qualitative signs of inadequate analgesia. An explicit Model Predictive Controller (MPC) was designed to achieve the above mentioned goals. The results of clinical tests of the controller on humans are presented and discussed.

Keywords **- Closed-loop Control, Model Predictive Control (MPC), Analgesia, Alfentanil, Mean Arterial Pressure (MAP).**

1 Introduction

Closed-loop administration of analgesic drugs may be used to improve the patient care by titrating drug delivery to specific and monitorable clinical end-points and to relieve the anesthesiologist from routine tasks. However, there is no agreement on the clinical end-point to which analgesic drugs should be titrated [3]. According to the International Association for the Study of Pain, pain is an 'unpleasant *sensory* and *emotional* experience associated with actual or potential tissue damage'. This means that it may be improper to talk about pain during general anesthesia when the patient is unconscious [7]. Nevertheless, opiates are routinely administered intraoperatively to decrease autonomic stress reactions to surgical stimulation [1, 6], such as Mean Arterial Pressure (MAP) and Heart Rate (HR) increases. These reactions must be minimized during surgery for the benefit of the patient [9].

Clinically, it may not be feasible to use a Single Input Single Output (SISO) controller to regulate MAP with opiates because of several reasons. First, opiates do not necessarily decrease MAP. They can if the MAP is elevated because of pain. Second, ceiling doses of opiates are not able to completely suppress the MAP reactions to surgical stimulation [5, 8]. Overdosing leads to prolonged respiratory depression and therefore long extubation times [10]. Finally, other qualitative signs of inadequate analgesia such as sweating and lacrimation are also considered in practice.

We developed an automatic control system to administer analgesic drugs during general anesthesia. We chose MAP as the main indicator of analgesia and the drug concentration in the plasma as a second indicator. Regulation of MAP must have priority over tracking plasma concentration. The controller must aim at maintaining both output variables within the constraints specified by the anestesiologist. Further, it must react with higher aggressiveness upon violation of the constraints.

To reach the above mentioned goals, we designed an explicit Model Predictive Controller (MPC). The two outputs of the system are predicted plasma concentration and measured MAP values. The manipulated input is the infusion rate of alfentanil. Since one of the outputs of the system is a variable predicted by a model, the controller realizes a tradeoff between a closed-loop analgesic administration to regulate MAP and an open-loop policy to target drug plasma concentrations. In this paper, we will first focus on the controller tuning and design. Then we will present and discuss the results of clinical studies where the controller was tested on patients.

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Abstract

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Fig. 1 depicts the block diagram of the control system used to regulate MAP and predicted plasma concentration of alfentanil. P represents the patient, whose measured MAP was denoted as y_2. M is a dynamic PK model used to predict drug concentration in the plasma y_1 depending on the patient's weight and height. C represents the MPC controller which computes the infusion rate of the pump u. K is the observer including an algorithm to reject MAP artifacts. $\hat{x}$ represents the observer states, which are the drug concentrations in the different compartments plus an additive disturbance to compensate for MAP reactions to surgical stimulation. $y_{1,ref}$ and $y_{2,ref}$ are plasma concentration and MAP references, respectively.

A linearized PK-PD model to predict the future output estimates of the drug's plasma concentration and MAP was adopted as an internal model in the MPC algorithm. The PK part consists of a three compartment model whose parameters were adapted from the published literature to match measured plasma concentrations collected during a clinical study on volunteers [4]. The PD part consists of an effect compartment linked to the central compartment of the PK model.

At every sampling time k the MPC controller computes the next m infusion rates $\{u(k|k, ..., u(k+m-1|k)\}$ which minimize the following objective function:

$$\begin{aligned} J = & \sum_{i=0}^{p-1} w^u ||u(k+i|k)||^2 + \\ & + w^{\Delta u} ||\Delta u(k+i|k)||^2 + \\ & + w^{y_1} ||[y_1(k+i+1|k) - y_{1,ref}(k+i+1)]||^2 + \\ & + w^{y_2} ||[y_2(k+i+1|k) - y_{2,ref}(k+i+1)]||^2 + \\ & + \rho_\epsilon \epsilon^2 \end{aligned} \tag{1}$$

subject to the following input and output constraints:

$$u_{min} < u < u_{max} \tag{2}$$

$$y_1 - y_{1,max} < \epsilon \cdot b_{1,max} \tag{3}$$

$$y_1 - y_{1,min} > -\epsilon \cdot b_{1,min} \tag{4}$$

$$y_2 - y_{2,max} < \epsilon \cdot b_{2,max} \tag{5}$$

$$y_2 - y_{2,min} > -\epsilon \cdot b_{2,min}. \tag{6}$$

The input moves are computed according to (1) to minimize the tracking error of MAP and predicted plasma concentrations, the drug infusion rate u and its rate of change Δu for the next p steps in the future. The violation of the constraints for the input and ouput variables is handled through the constraints in the optimization (2) - (6).

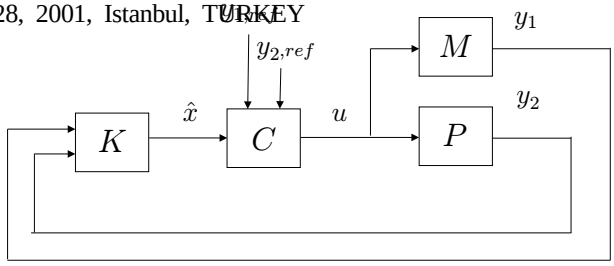

Figure 1: Block diagram of the explicit MPC controller.

The output constraints $\{y_{1,max}, y_{1,min}\}$ and $\{y_{2,max}, y_{2,min}\}$ can be chosen by the anesthesiologists according to the patient's cardiovascular conditions and the type of surgical procedure. The optimization weights $\{w^{\Delta u}, w^u, w^{y_1}, w^{y_2}, \rho_\epsilon\}$ were tuned to achieve the following clinical goals:

- regulation of MAP must have priority over tracking of plasma concentrations;
- the controller must keep MAP in a specified range around the reference value without aggressively tracking a specific value;
- the controller should react with marked aggressiveness when output constraints are violated.

The three requirements above were met by imposing $w^{y_1} < w^{y_2} < \rho_\epsilon$.
The weights $\{b_{1,max}, b_{1,min}, b_{2,max}, b_{2,min}\}$ determine the controller's tolerance upon constraint violation. Precisely, the lower the weight, the more aggressive will the controller be upon violation of that particular constraint. Constraint violations were ranked as follows from the most to the least severe:

1. hypotensive periods ($y_2 < y_{2,min}$)
2. overdosing ($y_1 > y_{1,max}$)
3. hypertensive periods ($y_2 > y_{2,max}$)
4. underdosing ($y_1 < y_{1,min}$).

According to the above ranking the weights for the constraint violation were selected by imposing $b_{2,min} < b_{1,max} < b_{2,max} < b_{1,min}$.

The controller is implemented in its explicit formulation. That is, the minimization problem (1) is translated into an equivalent piece-wise affine control algorithm [2]. This enables anesthesiologists to

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affects the controller's performance. The choice of the prediction horizons m and p affect the complexity of the explicit controller formulation. In order to minimize the complexity while guaranteeing adequate performance we set $p = 10$ and $m = 3$.

Since MAP measurements are acquired in our studies through an invasive catheter, they are often corrupted by artifacts. A supervisory system was designed to reject measurement artifacts from the closed-loop algorithm, which makes the controller applicable in the OR.

3 Clinical validation

Fig. 2 depicts the closed-loop performance of the controller during a hernia removal on a 49 years old female. The patient reacted very sensitively to both surgical stimulation and alfentanil. The strong raise of MAP due to the stimulations at $t = 109, 120, 137, 150, 169$ min triggered controller reactions comparable to manually administered bolus doses. MAP decreased sharply after each raise in the predicted concentrations. A MAP artifact at $t = 162$ min was correctly detected and did not trigger any harmful controller reaction.

Fig. 3 depicts the controller behaviour during the central phase of a lumbar hernia removal performed on a 37 years old woman. At $t = 170$ min

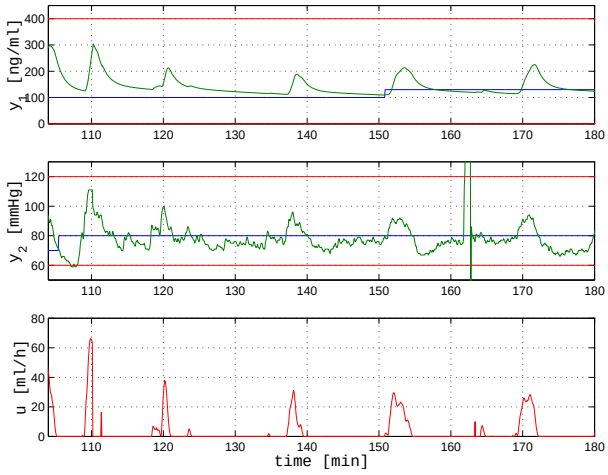

Figure 2: Closed-loop performance during surgery of the MAP controller. In the upper and middle plots, predicted plasma concentrations y_1 and MAP values y_2 are represented together with the output constraints and the reference values, respectively. In the lower plot, the infusion rate u is depicted.

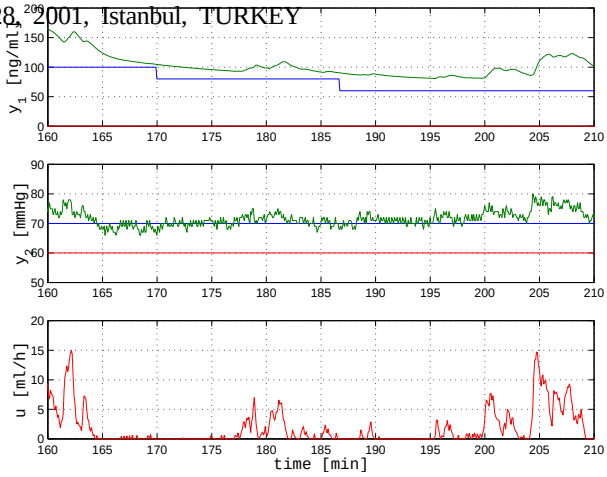

Figure 3: Closed-loop performance during surgery of the MAP controller. For a detailed description of the contents of each plot, refer to the caption of Fig. 2.

MAP and the predicted concentration were equal to their respective reference values. After $t = 170$ min and $t = 187$ min, $y_{2,ref}$ was decreased to 80 and 60 ng/ml, respectively. The anesthesiologist wanted to test whether the same adequate control performance could be achieved with lower analgesic concentrations in the plasma. The controller was able to perform adequately with respect to MAP regulation with lower plasma concentrations from $t = 170$ min to $t = 200$ min. MAP increased again during skin closure, which occurred at $t = 203$ min. The controller reacted leading to higher plasma concentrations, since MAP regulation has a higher priority in the controller design.

Fig. 4 depicts the behaviour of the controller during a spinal cord surgery performed on a 41 years old male. During the whole period MAP and drug plasma concentration were higher than their reference values. The control algorithm must increase the infusion rate because of the high MAP but at the same time it must decrease it because of the high plasma concentration. The controller realized a trade-off between the two incompatible objectives by targeting an almost constant plasma concentration which compensates for the high MAP. This concentration depends on the optimization weights on MAP and plasma concentration in the objective function (1). Particularly, between $t = 160$ min and $t = 180$ min the MAP stayed constantly about 15 mmHg above the reference value. The controller adjusted the infusion rates in such a way that the plasma concentrations stayed constantly about 100 ng/ml above the reference value. At $t = 185$ min a strong surgical stimulus triggered a strong MAP reaction resulting

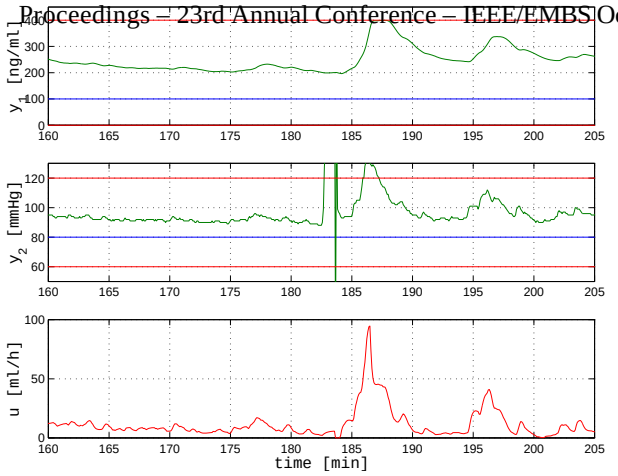

Figure 4: Closed-loop performance during surgery of the MAP controller. For a detailed description of the contents of each plot, refer to the caption of Fig. 2.

in MAP values beyond the upper constraints for approximately 2 min. The controller reacted with a high infusion rate resulting in a plasma concentration equal to the upper constraint. Since the weight on the upper constraint for plasma concentration is higher than the one on the upper MAP constraint the controller did not allow plasma concentrations to go beyond 400 ng/ml.

4 Conclusions

We presented a new paradigm for the the closed-loop administration of analgesic drugs during surgery. MAP was used as the main indicator of the analgesic state of the patient. The use of predicted plasma concentrations of the analgesic as a second output to be controlled enabled the anesthesiologists to titrate drug administration to alternative signs of inadequate analgesia and to prevent overdosing. We chose a MPC approach to regulate MAP and predicted concentrations of alfentanil, realizing a user definable trade-off between closed-loop control to regulate MAP and open-loop targeting policy of drug plasma concentrations. The MPC algorithm enabled us to handle the different output constraints with different controller aggressiveness.

A major critique may be moved to the approach presented here. Adjusting the infusion rate of opiates solely on the basis of MAP neglects important other patient information such as Heart Rate (HR), Cardiac Output (CO) and Bispectral Index (BIS). The presence of predicted plasma concentrations as a second output of the system partially compensated for the perceived oversimplification.

We presented and discussed the results of three clinical studies which were performed at the University Hospital in Bern. The controller showed satisfactory results in the OR. MAP reactions to surgical stimuli were compensated by the controller's reactions. When MAP lied in a satisfactory range around the reference value, the controller was successfully tracking the predicted plasma concentration provided by the anesthesiologists. Finally, the controller was able to react promptly upon violation of the output constraints.

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